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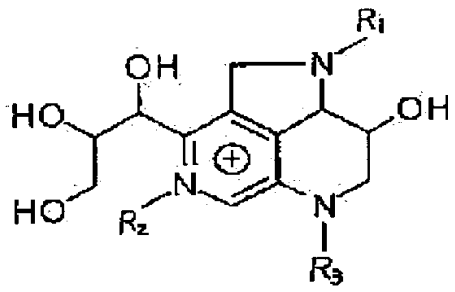
(71)Applicant : NIPPON ZOKI PHARMACEUT CO LTD
(72)Inventor : NAKAZAWA YOSHITAKA
NAKAMURA KO

(54) PYRROLONAPHTHYRIDINIUM DERIVATIVE

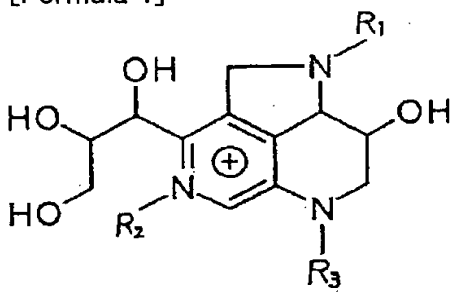
(57)Abstract:
PROBLEM TO BE SOLVED: To obtain the subject new compound useful for diagnosing diabetes (complications), complications related to dialysis, amyloidosis, aging, diseases, etc., associated with the aging or evaluating pharmacodynamic effects of a medicine effective against the diseases, etc.
SOLUTION: This compound is represented by the formula {R1 to R3 are each a [(protected) amino or carboxy-substituted]alkyl} or its salt, e.g. 8- hydroxy-1,2,6,7,8,8a-hexahydro-3-(1,2,3-trihydroxypropyl)-1,4,6tris(3-carboxypropyl)- pyrrolo[2,3,4-de][1,7]naphthyridinium. The compound represented by the formula is obtained by the coexistence of an amine component represented by the formula R1-NH2, R2-NH2 or R3-NH2 with saccharides such as a hexose, an aminosugar or an oligosaccharide.



* NOTICES *

CLAIMS

[Serial Number] PC-260. [Claim(s)]
[Claim 1] The pyrrolo NAFUCHIRIJINIUMU derivative expressed with a general formula (I), and its salt.
[Formula 1]



(I)

R1, R2, and R3 express respectively the same or the alkyl group which may have the amino group which differ and has an amino group and a protective group, and/or a carboxyl group among [formula.]
[Claim 2] The antibody created considering the pyrrolo NAFUCHIRIJINIUMU derivative expressed with the above-mentioned general formula (I) as a hapten.
[Claim 3] Diagnostics of the disorder accompanying the diabetes which made the index the pyrrolo NAFUCHIRIJINIUMU derivative expressed with the above-mentioned general formula (I), diabetic complications, a dialysis related complication, amyloidosis, aging, and aging.
[Claim 4] Diagnostics of the disorder accompanying the diabetes using the antibody created considering the pyrrolo NAFUCHIRIJINIUMU derivative expressed with the above-mentioned general formula (I) as a hapten, diabetic complications, a dialysis related complication, amyloidosis, aging, and aging.
[Claim 5] The pharmacometrics method of the diabetes therapeutic drug which made the index the pyrrolo NAFUCHIRIJINIUMU derivative expressed with the above-mentioned general formula (I), a diabetic-complications therapeutic drug, a dialysis related complication therapeutic drug, an amyloidosis therapeutic drug, aging prevention medicine, and the disorder therapeutic drug accompanying aging.
[Claim 6] The pharmacometrics method of the diabetes therapeutic drug using the antibody created considering the pyrrolo NAFUCHIRIJINIUMU derivative expressed with the above-mentioned general formula (I) as a hapten, a diabetic-complications therapeutic drug, a dialysis related complication therapeutic drug, an amyloidosis therapeutic drug, aging prevention medicine, and the disorder therapeutic drug accompanying aging.

[Translation done.]

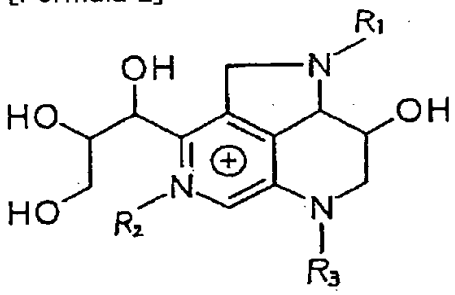
* NOTICES *

1. This document has been translated by computer.So the translation may not reflect the original precisely.
2. **** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[The technical field to which invention belongs] this invention relates a new pyrrolo NAFUCHIRIJINIUMU derivative and this derivative to the pharmacometrics method of a medicine effective in diagnostics, such as a disease accompanying the diabetes using the antibody created as a hapten and this derivative, or its antibody, diabetic complications, a dialysis related complication, amyloidosis, aging, and aging, or those diseases.
[0002]
[Description of the Prior Art] The GURIKO sill hemoglobin (HbA1c) which is the small component of hemoglobin is identified in the living body, it becomes clear that this increases in a diabetic, and the relation between the living thing-meaning of a Maillard reaction especially aging, and diabetes has come to attract attention ignited by it in 1968. A Maillard reaction is distinguishable to two, an initial stage until the amino group of protein and the aldehyde group of reducing sugar cause and stabilize AMADORI transition after forming a Schiff base, and the later stage which shifts to a product (AGE) in the second half of a Maillard reaction when this is characterized by fluorescence, brown change, and molecule bridge formation through a further long-term reaction. The fluorescence nature known as characteristic change of AGE is [healthy person / diabetic] intentionally high, and the development of symptoms and functionality of **** of diabetes nature, arteriosclerosis, neuropathy, ******, ******, etc. which are a diabetic complication are suggested. Furthermore, recently, the scavenger receptor which recognizes AGE protein exists in a monocyte, a macrophage, a MESANGIUMU cell, or an endothelial cell, and there is also report which suggests the relevance of AGE and symptoms, such as inflammation, capillary lock out, and arteriosclerosis, that the AGE recognition through these acceptors causes cytokine discharge etc. Moreover, the fluorescence of the protein accumulated in a blood serum increases during dialysis, and the relation of AGE and dialysis related amyloidosis is also pointed out.
[0003]
[Problem(s) to be Solved by the Invention] Although several sorts of AGE candidate matter is mentioned until now and those structures are being analyzed, the present condition is that still unknown points, such as existence of existence in the living body, a difference in immunochemistry-activity, and relevance with actual symptoms, remain mostly. Unlike the conventional monoamine and the diamine compound, this invention persons found out the new pyrrolo NAFUCHIRIJINIUMU derivative which is the triamine compound which is not reported at all until now, as a result of thinking that important AGE from which structure differs besides the candidate matter reported so far will exist and continuing research about AGE further.
[0004]
[Means for Solving the Problem] The purpose of this invention is to offer the pharmacometrics method of a medicine effective in diagnostics, such as a disease accompanying the diabetes using the antibody created considering the new pyrrolo NAFUCHIRIJINIUMU derivative and this derivative as a hapten and this derivative, or its antibody, diabetic complications, a dialysis related complication, amyloidosis, aging, and aging,

or those diseases.
[0005]
[Embodiments of the Invention] this invention new pyrrolo NAFUCHIRIJINIUMU derivative is a compound expressed with the following general formula (I).
[Formula 2]



(I)

R1, R2, and R3 express respectively the same or the alkyl group which may have the amino group which differ and has an amino group and a protective group, and/or a carboxyl group among [formula.]
R1 of the above-mentioned general formula (I), and R2 And R3 As an alkyl group which can be set, the carbon number 1 of straight chains, such as a methyl, ethyl, a propyl, an isopropyl, butyl, an isobutyl, sec-butyl, t-butyl, a pentyl, an isopentyl, neopentyl one, t-pentyl, a hexyl, and dimethyl butyl, or the letter of branching or the alkyl group of 6 is mentioned preferably.
[0006] The aforementioned alkyl group may have the amino group and/or carboxyl group which have an amino group and a protective group. as a protective group of the amino group The protective group usually used in fields, such as peptide synthesis chemistry, can be used. For example, an acetyl, a benzyloxycarbonyl, p-methoxybenzyloxy carbonyl, p-chloro benzyloxycarbonyl, p-nitroglycerine benzyloxycarbonyl, p-phenylazo benzyloxycarbonyl, p-methoxy phenylazo benzyloxycarbonyl, Bases, such as t-butoxycarbonyl (Boc), p-tosyl (Tos), the third friend ROKISHI carbonyl, p-biphenyl isopropyloxy carbonyl, diisopropyl MECHIROKISHIKABONIRU, and HORUMIRU, are mentioned.
[0007] In this invention matter expressed with a general formula (I), it is R1 and R2. And R3 The pyrrolo NAFUCHIRIJINIUMU derivative which is the alkyl group which has an amino group and/or a carboxyl group is useful, especially when it can be made to combine with a carrier protein etc. easily as a hapten and an antibody is created. As support combined with a hapten in order to create an antibody, support usually used, such as polymer, such as protein, such as a serum albumin and limpet blood-pigment protein, and the poly lysine, can be used.
[0008] this invention pyrrolo NAFUCHIRIJINIUMU derivative includes the salt expressed with the aforementioned general formula (I). For example, a hydrochloric acid, a sulfuric acid, a nitric acid, a hydrobromic acid, a phosphoric acid, perchloric acid, a thiocyanic acid, A boric acid, a formic acid, an acetic acid, a halo acetic acid, a propionic acid, a glycolic acid, a citric acid, A tartaric acid, a succinic acid, a gluconic acid, a lactic acid, a malonic acid, a fumaric acid, an anthranilic acid, A benzoic acid, a cinnamic acid, p-toluenesulfonic acid, a naphthalene sulfonic acid, A salt with a metal with alkaline earth metal, such as alkali metal, such as an addition salt with organic bases, such as an addition salt with an acid with a sulfanilic acid etc., ammonia, and an organic amine, or sodium, and a potassium, calcium, magnesium, and barium, or aluminum, zinc, etc. is mentioned. These salts can be manufactured from this invention pyrrolo NAFUCHIRIJINIUMU derivative of isolation by the well-known method, or can be changed mutually.
[0009] Moreover, when stereoisomers, such as a SHISU-transformer object, an optical isomer, and a conformer, exist in this invention compound, or when it exists in the state of a hydrate or a complex compound, this invention also includes which the stereoisomer, a hydrate, and a complex compound.

[0010] Next, an example of the manufacture method of this invention compound is described. R1-NH2 and R2-NH2 Or R3-NH2 this invention compound can be obtained by making the compound (amine component: -- R1, R2, and R3 expressing the same machine as the each above) expressed coexist with saccharides, such as oligosaccharides, such as aminosugars, such as hexoses, such as a glucose, fructose, a galactose, a mannose, and a deoxy glucose, a glucosamine, and a galactosamine, and a saccharose. Moreover, after carrying out a mixed reaction, using protein and peptides as an amine component, acidolysis processing can be performed and this invention compound can also be obtained.
[0011] About reaction conditions, such as reaction temperature, reaction time, and pH, there are no special setups and they can be set up suitably. Although what is necessary is just to leave easy one in the room temperature on operation, a reaction can be promoted by heating etc. The usual meanses, such as distillation, a chromatography, and recrystallization, can refine the obtained this invention compound.
[0012]
[Example] this invention is not limited by this although the example of this invention pyrrolo NAFUCHIRIJINIUMU derivative is shown below.
Example 1. glucose 79.2g and 45.3g (GABA) of gamma aminobutyric acid were dissolved in 1100ml (pH 7.3) of 250mM phosphate buffer solutions, and it put for 45 days at 37 degrees C. The reaction solution was added to a sulfonic-acid mold cation exchange resin / DIAION PK-216 (Mitsubishi Kasei), it was [bottom 40 degree-C of reduced pressure] under water bath, and concentration hardening by drying of the solution eluted with 2-N aqueous ammonia was carried out after rinsing. AMBERLITE XAD-2 which equilibrated by ion exchange water after dissolving a hardening-by-drying object in little ion exchange water It added in the column (ORGANO CORP.) and passage fractions were collected. DEVELOSIL ODS LOP-45S after condensing this fraction It added in the column (Nomura chemistry) and was eluted in the methanol-trifluoroacetic-acid mixed solution. Furthermore, separation refining of this was carried out by the reversed phase high pressure liquid chromatography / STR ODS-II column (Shimazu techno research), and the compound 1 (65mg), the compound 2 (182.9mg), and compound 3 (35.5mg) which are a stereoisomer were isolated, respectively.
[0013] Example 2. glucose 25.2g and alpha-acetyl lysine 34g were dissolved in 700ml of 250mM phosphate buffer solutions, the same operation as an example 1 was performed, and the compound 4 (2mg) and compound 5 (3mg) which are a stereoisomer were isolated, respectively.
[0014] The physical-properties value of the obtained this invention compound is shown below. In addition, the 1st place or the total carbon manufactured the quality of a label ghost using the glucose by which the label was carried out by 13C by the same method as the above-mentioned example, and it used for structural analysis. Fluorescence spectrum Both ultraviolet-region absorption (UV) spectrums were measured in the methanol by DU-650 (Beckman) with 650-40 Fluorescence Spectrophotometer (Hitachi). Spatter DOION mass analysis PEKUTORU (SIMS) The glycerol was used for the matrix by M-80B (Hitachi), and it measured. The nuclear-magnetic-resonance (NMR) spectrum was measured by ARX-500 (Bruker) among heavy water, and, in the proton, 13C set 125.77MHz of resonance frequencies to 0.00 ppm for 500.13MHz of resonance frequencies. Attribution of 1 H-NMR spectrum and 13 C-NMR spectrum 1H-1H Two-dimensional NMR, such as COSY and HMQC, determined.
[0015] - compound 18-hydroxy-1, 2, 6, 7 and 8, and 8a-hexahydro-3-(1, 2, 3-trihydroxy propyl)- 1, 4, and 6-tris (3-carboxy propyl)-pyrrolo [2, 3, 4-de] [1, 7] NAFUCHIRIJINIUMU fluorescence-spectrum:EXmax = 370 nm, EMmax = 450 nmUV spectrum:lambdamax = 237, 276, 360 nmSIMS:m/z 5271 H-NMR(D2O)-deltappm: 1.79 (2H, m, H-2‴) 2.04 (2H, m, H-2'), 2.13 (2H, m, H-2″) 2.33 (2H, t, J= 7Hz, H-3‴), 2.44 (4H, t, J= 7Hz, H-3', 3″) 3.35 (2H, m, H-1‴), 3.47 (1H, m, H-1') 3.50 (1H, dd, J = 14 or 2Hz, H-7), 3.59 (1H, m, H-1') 3.63-3.69 (4H, m, H-7, 10, 11, 11), 4.33 (1H, m, H-1″) 4.68 (1H, brs, H-8), 4.68 (1H, m, H-1″) 4.83 (1H, d, J= 14Hz, H-2), 4.98 (1H, d, J= 1Hz, H-8a) 5.20 (1H, d, J= 9Hz, H-9), 5.36 (1H, dd, J = 14 or 1Hz, H-2), 7.92 (1H, s, H-5) 13 C-NMR(D2O)-deltappm : 22.2 (t, C-2', 2‴), 27.1 (t, C-2″), 31.5 (t, C-3‴), 32.2 (t, C-3'), 33.3 (t, C-3″), 49.4 (t, C-1‴), 53.5 (t, C-7), 54.5 (t, C-1'), 58.6 (d, C-8),

59.8 (t, C-2, 1″), 63.2 (t, C-11), 67.3 (d, C-8a), 68.6 (d, C-9), 74.6 (d, C-10), 126.8 (d, C-5), 134.6 (s and C-2a), 135.3 (s and C-8b), 139.7 (s, C-3), 140.8 (s and C-5a), 178.8 (s, C-4‴), 180.2 (s and C-4', 4″) [0016] - compound 28-hydroxy-1, 2, 6, 7 and 8, and 8a-hexahydro-3-(1, 2, 3-trihydroxy propyl)- 1, 4, and 6-tris (3-carboxy propyl)-pyrrolo [2, 3, 4-de] [1, 7] NAFUCHIRIJINIUMU fluorescence-spectrum:EXmax = 370 nm, EMmax = 450nmUV spectrum:lambdamax = 240, 277, 360 nmSIMS:m/z 5271 H-NMR(D2O)-deltappm: 1.82 (2H, m, H-2‴), 2.06 (2H, m, H-2') 2.12 (2H, m, H-2″), 2.35 (2H, t, J= 7Hz, H-3‴) 2.46 (4H, t, J= 7Hz, H-3', 3″), 3.33 (1H, ddd, J= 14, 7 or 7Hz, H-1‴), 3.42 (1H, ddd, J= 14, 7 or 7Hz, H-1‴), 3.48 (1H, m, H-1') 3.49 (1H, dd, J = 14 or 2Hz, H-7), 3.61 (1H, m, H-1') 3.68 (1H, dd, J = 14 or 1Hz, H-7), 3.69 (1H, ddd, J= 9, 3 or 3Hz, H-10) 3.73 (1H, dd, J = 3 or 3Hz, H-11), 3.76 (1H, dd, J = 3 or 3Hz, H-11) 4.39 (1H, m, H-1″), 4.68 (1H, d, J= 2Hz, H-8) 4.79 (1H, m, H-1″), 4.89 (1H, d, J= 14Hz, H-2) 5.01 (1H, d, J= 2Hz, H-8a), 5.06 (1H, d, J= 14Hz, H-2) 5.21 (1H, d, J= 9Hz, H-9), 7.95 (1H, s, H-5) 13 C-NMR(D2O)-deltappm: 21.8 (t, C-2‴), 22.2 (t, C-2'), 26.8 (t, C-2″), 31.5 (t, C-3‴), 31.8 (t, C-3'), 32.0 (t, C-3″), 49.8 (t, C-1‴), 53.9 (t, C-7), 54.3 (t, C-1'), 58.8 (t, C-1″), 60.4 (d, C-8), 61.1 (t, C-2), 63.7 (t, C-11), 67.7 (d, C-8a), 69.0 (d, C-9), 74.8 (d, C-10), 127.3 (d, C-5), 134.5 (s and C-2a), 135.1 (s and C-8b), 141.1 (s, C-3, 5a), 178.0 (s and C-4', 4‴), 178.8 (s and C-4″) [0017] - compound 38-hydroxy-1, 2, 6, 7 and 8, and 8a-hexahydro-3-(1, 2, 3-trihydroxy propyl)- 1, 4, and 6-tris (3-carboxy propyl)-pyrrolo [2, 3, 4-de] [1, 7] NAFUCHIRIJINIUMU fluorescence-spectrum:EXmax = 373 nm, EMmax = 452 nmUV spectrum:lambdamax = 239, 278, 360 nmSIMS:m/z 5271 H-NMR(D2O)-deltappm: 1.84 (2H, m, H-2‴) 2.03 (2H, m, H-2'), 2.12 (2H, m, H-2″) 2.35 (2H, t, J= 7Hz, H-3‴), 2.46 (4H, m, H-3', 3″) 3.31 (1H, ddd, J= 14, 7 or 7Hz, H-1‴), 3.39 (1H, ddd, J= 14, 7 or 7Hz, H-1‴), 3.46 (1H, dd, J = 14 or 1Hz, H-7) 3.50 (1H, m, H-1'), 3.78 (1H, dd, J = 14 or 3Hz, H-7) 3.70-3.79 (4H, m, H-10, 11 and 11, 1'), 4.32 (2H, m, H-8, 1″) 4.78 (1H, m, H-1″), 4.79 (1H, d, J= 10Hz, H-8a) 4.83 (1H, d, J= 14Hz, H-2), 5.08 (1H, d, J= 14Hz, H-2) 5.22 (1H, d, J= 9Hz, H-9), 7.93 (1H, s, H-5) 13 C-NMR(D2O)-deltappm: 21.8 (t, C-2‴), 22.1 (t, C-2'), 26.6 (t, C-2″), 31.3 (t, C-3‴), 31.6 (t, C-3'), 31.8 (t, C-3″), 49.6 (t, C-1‴), 54.0 (t, C-7), 55.7 (t, C-1'), 60.2 (t, C-2), 60.4 (t, C-1″), 63.5 (t, C-11), 63.9 (d, C-8), 69.0 (d, C-9), 70.4 (d, C-8a), 74.7 (d, C-10), 127.7 (d, C-5), 134.1 (s and C-2a), 135.2 (s and C-8b), 141.4 (s and C- 5a, 3), 177.7 (s, C-4‴), 177.7 (s and C-4'), 178.8 (s and C-4″) [0018] - compound 48-hydroxy-1, 2, 6, 7 and 8, and 8a-hexahydro-3-(1, 2, 3-trihydroxy propyl)- 1, 4, and 6-tris [6-(N-acetyl-L-NORUROISHIRU)]-pyrrolo [2, 3, 4-de] [1, 7] NAFUCHIRIJINIUMU fluorescence-spectrum:EXmax = 374 nm, EMmax = 452 nmUV spectrum:lambdamax = 237, 277, and 360 nmSIMS:m/z 7821 H-NMR(D2O)-deltappm: 1.40 (6H, m, H-3', 3″, and 3″ -- ') -- 1.68 (2H, m, H-2‴) 1.72 (4H, m, H-2', 2″), 1.84 (6H, m, H-4', 4″, and 4″ -- ') and 1.98 (3H, s, AcO‴-Me) -- 1.99 (3H, s, AcO'-Me) 2.00 (3H, s, AcO″-Me), 3.41 (1H, m, H-1') 3.53 (2H, m, H-1‴), 3.61 (1H, dd, J = 14 or 1Hz, H-7) 3.62 (1H, m, H-1'), 3.74 (1H, dd, J = 14 or 1Hz, H-7) 3.79 (11 3H, m, H-10, 11), 4.23 (3H, m, H-5', 5″, and 5″ -- ') and 4.42 (1H, m, H-1″) -- 4.70 (1H, s, H-8) 4.70 (1H, m, H-1″), 4.89 (1H, d, J= 14Hz, H-2) 5.07 (1H, d, J= 1Hz, H-8a), 5.22 (1H, d, J= 9Hz, H-9) 5.41 (1H, dd, J = 14 or 1Hz, H-2), 7.95 (1H, s, H-5) 13 C-NMR(D2O)-deltappm: 22.6 (q, AcO'-Me, AcO″-Me, AcO‴-Me), -- 22.8 (t, C-2') and 23.1 (t and C-2 -- ‴, 3', 3″ -- ') -- 25.4 (t, C-3″), 26.0 (t, C-2″), 30.8 (t, C-4'), 30.9 (t, C-4‴) 31.3 (t, C-4″) 49.9 (t, C-1'), 53.4 (d, C-5', 5‴) 53.6 (d, C-5″), 54.6 (t, C-7, 1‴), 58.5 (d, C-8), 60.5 (t, C-1″), 60.8 (t, C-2), 63.1 (t, C-11), 67.3 (d, C-8a), 68.6 (d, C-9), 74.4 (d, C-10), 126.6 (d, C-5), 134.0 (s and C-2a), 134.3 (s and C-8b), 140.1 (s, C-3), 140.7 (s and C-5a), 175.1 (s and C-6'), 175.1 (s, C-6‴), 175.2 (s and C-6″), 176.6 (s and AcO'-CO), 176.7 (s, AcO‴-CO), 176.8 (s, AcO″-CO) [0019] - compound 58-hydroxy-1, 2, 6, 7 and 8, and 8a-hexahydro-3-(1, 2, 3-trihydroxy propyl)- 1, 4, and 6-tris [6-(N-acetyl-L-NORUROISHIRU)]-pyrrolo [2, 3, 4-de] [1, 7] NAFUCHIRIJINIUMU fluorescence-spectrum:EXmax = 376 nm, EMmax = 452 nmUV spectrum:lambdamax = 239, 278, and 360 nmSIMS:m/z 7821 H-NMR(D2O)-deltappm: 1.39-1.48 (6H, m, H-3', 3″, and 3″ -- ') -- 1.66 (2H, m, H-2‴) 1.73 (4H, m, H-2', 2″), 1.89 (6H, m, H-4', 4″, and 4″ -- ') and 1.98 (3H, s, AcO‴-Me) -- 1.98 (3H, s, AcO'-Me) 2.00 (3H, s, AcO″-Me), 3.39 (1H, m, H-1‴) 3.44 (1H, m, H-1‴), 3.50 (1H, m, H-1') 3.57 (1H, dd, J = 14 or 2Hz, H-7), 3.65 (1H, m, H-1') 3.73 (1H, dd, J = 14 or 1Hz, H-7), 3.81 (11 3H, m, H-10, 11) and 4.27-4.35 (four -- H -- m -- H - one -- ″ -- five -- ' -- five -- ″ -- five -- ″ -- ') -- 4.75 (1H,

brs, H-8) 4.78 (1H, m, H-1″), 4.94 (1H, d, J= 14Hz, H-2), 5.08 (1H, brs, H-8a), 5.09 (1H, dd, J = 14 or 1Hz, H-2), 5.20 (1H, d, J= 9Hz, H-9), 7.95 (1H, s, H-5) [0020]
[Effect of the Invention] Some candidate matter is reported as a AGE until now, and research is also advanced now. Although this invention person and its associate had also found out a pyridinium derivative and a NAFUCHIRIJINIUMU derivative which are indicated by JP,6-73057,A and JP,8-48686,A, these made the condensation 2 ring system of a diamine the basic mother nucleus. Unlike the conventional compound, this invention pyrrolo NAFUCHIRIJINIUMU derivative should make the condensation 3 ring system of triamine a basic mother nucleus, and should be observed very much as completely new AGE candidate matter from the new structure of a flume lie with three parts in which bridge formation with protein in the living body is possible.
[0021] Therefore, like the AGE compound reported conventionally, this invention compound is made into an index, a diagnosis of diabetic complication, such as diabetes and diabetic nephropathy, diabetes nature arteriosclerosis, a diabetic neuropathy, diabetic cataract, diabetic retinopathy, and a diabetes nature microangiopathy, and aging, the disorder accompanying it, etc. is possible, and pharmacometrics etc. can be further performed by making this invention compound into an index in in vitro one and an in vivo examination system. Moreover, the antibody created as a hapten can use this invention compound immunochemistry-wise and in immunohistochemistry in the above-mentioned diagnosis or pharmacometrics, and usefulness is very high. As mentioned above, known AGE is new matter which is the condensation 3 ring system skeleton of clearly different triamine, the existence [in the living body] and biological activity different from the old AGE candidate matter are suggested, and this invention pyrrolo NAFUCHIRIJINIUMU derivative can also expect different usefulness.

[Translation done.]

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(71)出願人　000231796
日本臓器製薬株式会社
大阪府大阪市中央区平野町2丁目1番2号

(72)発明者　中澤　良隆
兵庫県加東郡社町木梨字川北山442番1　日本臓器製薬株式会社生物活性科学研究所内

(72)発明者　中村　耕
兵庫県加東郡社町木梨字川北山442番1　日本臓器製薬株式会社生物活性科学研究所内

(74)代理人　弁理士　村山　佐武郎

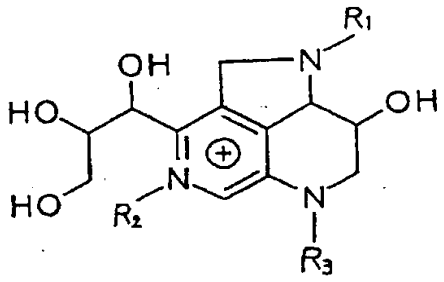
(54)【発明の名称】ピロロナフチリジニウム誘導体

(57)【要約】　(修正有)

【課題】糖尿病、糖尿病合併症、透析関連合併症、アミロイドーシス、老化、老化に伴う疾患等の診断などに有効な新規なピロロナフチリジニウム誘導体及び該誘導体をハプテンとして作成された抗体を提供する。

【解決手段】本発明ピロロナフチリジニウム誘導体は次の一般式で表される新規化合物である。

【化１】



(I)

〔式中、R_1、R_2及びR_3は各々同一若しくは異なってアミノ基、保護基を有するアミノ基及び／又はカルボキシル基を有してもよいアルキル基を表す。〕

【効果】本発明化合物を指標として、糖尿病、糖尿病合併症、透析関連合併症、アミロイドーシス、老化、老化に伴う疾患等の診断が可能であり、またそれら疾患等に有効な薬剤の薬効評価法に利用することもできる。

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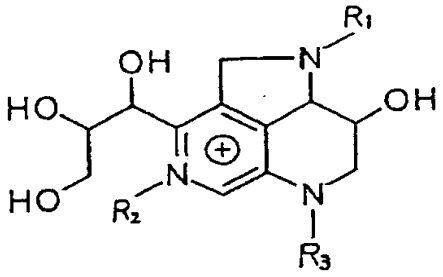
【整理番号】　　ＰＣ－２６０

【特許請求の範囲】

【請求項１】　一般式（Ｉ）で表されるピロロナフチリジニウム誘導体及びその塩。

【化１】



（Ⅰ）

〔式中、R_1、R_2及びR_3は各々同一若しくは異なってアミノ基、保護基を有するアミノ基及び／又はカルボキシル基を有してもよいアルキル基を表す。〕

【請求項２】　上記一般式（Ｉ）で表されるピロロナフチリジニウム誘導体をハプテンとして作成された抗体。

【請求項３】　上記一般式（Ｉ）で表されるピロロナフチリジニウム誘導体を指標とした糖尿病、糖尿病合併症、透析関連合併症、アミロイドーシス、老化、老化に伴う疾患の診断法。

【請求項４】　上記一般式（Ｉ）で表されるピロロナフチリジニウム誘導体をハプテンとして作成された抗体を用いた糖尿病、糖尿病合併症、透析関連合併症、アミロイドーシス、老化、老化に伴う疾患の診断法。

【請求項５】　上記一般式（Ｉ）で表されるピロロナフチリジニウム誘導体を指標とした糖尿病治療薬、糖尿病合併症治療薬、透析関連合併症治療薬、アミロイドーシス治療薬、老化防止薬、老化に伴う疾患治療薬の薬効評価法。

【請求項６】　上記一般式（Ｉ）で表されるピロロナフチリジニウム誘導体をハプテンとして作成された抗体を用いた糖尿病治療薬、糖尿病合併症治療薬、透析関連合併症治療薬、アミロイドーシス治療薬、老化防止薬、老化に伴う疾患治療薬の薬効評価法。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、新規なピロロナフチリジニウム誘導体及び該誘導体をハプテンとして作成された抗体、並びに該誘導体又はその抗体を用いた糖尿病、糖尿病合併症、透析関連合併症、アミロイドーシス、老化、老化に伴う疾患等の診断法或いはそれらの疾患等に有効な薬剤の薬効評価法に関する。

【０００２】

【従来の技術】１９６８年、ヘモグロビンの小成分であるグリコシルヘモグロビン（ＨｂＡ１ｃ）が生体内で同

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定され、これが糖尿病患者において増加することが判明し、それを契機にメイラード反応の生物的意義、特に老化と糖尿病との関係が注目されるようになってきた。メイラード反応は蛋白のアミノ基と還元糖のアルデヒド基とがシッフ塩基を形成後、アマドリ転移を起こして安定化するまでの初期段階と、これがさらに長期の反応を経て、蛍光、褐色変化、分子架橋を特徴とするメイラード反応後期生成物（ＡＧＥ）に移行する後期段階の２つに区別できる。ＡＧＥの特徴的変化として知られている蛍光性は糖尿病患者では健常者に比べて有意に高く、また糖尿病の合併症である糖尿病性の腎症、動脈硬化症、神経障害、網膜症、白内症等の発症と相関性が示唆されている。更に最近では、単球、マクロファージ、メサンギウム細胞や内皮細胞にＡＧＥ蛋白質を認識するスカベンジャーレセプターが存在し、これらの受容体を介したＡＧＥ認識がサイトカイン放出等を引き起こすという、ＡＧＥと炎症、毛細血管閉塞、動脈硬化等の病態との関連性を示唆する報告もある。また、透析中に血清中に蓄積する蛋白の蛍光が増加し、ＡＧＥと透析関連アミロイドーシスとの関連も指摘されている。

【０００３】

【発明が解決しようとする課題】これまで数種のＡＧＥ候補物質が挙げられており、それらの構造は解析されつつあるが、生体内における存在の有無、免疫化学的活性の差異、実際の病態との関連性など未だ不明な点が多く残っているのが現状である。本発明者らは、これまで報告されてきた候補物質以外にも構造の異なる重要なＡＧＥが存在するのではないかと考え、更にＡＧＥに関して研究を続けた結果、従来のモノアミン、ジアミン化合物とは異なり、これまでに全く報告されていないトリアミン化合物である新規なピロロナフチリジニウム誘導体を見い出した。

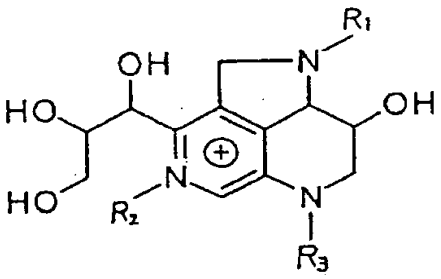
【０００４】

【課題を解決するための手段】本発明の目的は、新規なピロロナフチリジニウム誘導体及び該誘導体をハプテンとして作成された抗体、並びに該誘導体又はその抗体を用いた糖尿病、糖尿病合併症、透析関連合併症、アミロイドーシス、老化、老化に伴う疾患等の診断法或いはそれらの疾患等に有効な薬剤の薬効評価法を提供することにある。

【０００５】

【発明の実施の形態】本発明新規ピロロナフチリジニウム誘導体は次の一般式（Ｉ）で表される化合物である。

【化２】



(Ⅰ)

〔式中、R_1、R_2及びR_3は各々同一若しくは異なってアミノ基、保護基を有するアミノ基及び／又はカルボキシル基を有してもよいアルキル基を表す。〕

上記一般式（Ｉ）のR_1、R_2及びR_3におけるアルキル基としては、好ましくはメチル、エチル、プロピル、イソプロピル、ブチル、イソブチル、ｓｅｃ－ブチル、ｔ－ブチル、ペンチル、イソペンチル、ネオペンチル、ｔ－ペンチル、ヘキシル、ジメチルブチル等の直鎖又は分枝状の炭素数１乃至６のアルキル基が挙げられる。

【０００６】前記アルキル基は、アミノ基、保護基を有するアミノ基及び／又はカルボキシル基を有していてもよく、アミノ基の保護基としては、ペプチド合成化学等の分野で通常使用されている保護基が利用でき、例えば、アセチル、ベンジルオキシカルボニル、ｐ－メトキシベンジルオキシカルボニル、ｐ－クロロベンジルオキシカルボニル、ｐ－ニトロベンジルオキシカルボニル、ｐ－フェニルアゾベンジルオキシカルボニル、ｐ－メトキシフェニルアゾベンジルオキシカルボニル、ｔ－ブトキシカルボニル（Ｂｏｃ）、ｐ－トルエンスルホニル（Ｔｏｓ）、第三アミロキシカルボニル、ｐ－ビフェニルイソプロピルオキシカルボニル、ジイソプロピルメチロキシカボニル、ホルミル等の基が挙げられる。

【０００７】一般式（Ｉ）で表される本発明物質のなかで、R_1、R_2及びR_3がアミノ基及び／又はカルボキシル基を有するアルキル基であるピロロナフチリジニウム誘導体は、ハプテンとして担体蛋白質等と容易に結合させることができ、抗体を作成するときには特に有用である。抗体を作成するためにハプテンと結合させる担体としては、血清アルブミン、カサガイ血液色素蛋白質等の蛋白質やポリリジン等のポリマー類など通常使用されている担体類を用いることができる。

【０００８】本発明ピロロナフチリジニウム誘導体は、前記の一般式（Ｉ）で表される塩を包含し、例えば、塩酸、硫酸、硝酸、臭化水素酸、リン酸、過塩素酸、チオシアン酸、ホウ酸、ギ酸、酢酸、ハロ酢酸、プロピオン酸、グリコール酸、クエン酸、酒石酸、コハク酸、グルコン酸、乳酸、マロン酸、フマル酸、アントラニル酸、安息香酸、ケイ皮酸、ｐ－トルエンスルホン酸、ナフタレンスルホン酸、スルファニル酸等との酸との付加塩、

アンモニア、有機アミン等の有機塩基との付加塩、或いはナトリウム、カリウム等のアルカリ金属、カルシウム、マグネシウム、バリウム等のアルカリ土類金属又はアルミニウム、亜鉛等との金属との塩などが挙げられる。これらの塩は公知の方法により遊離の本発明ピロロナフチリジニウム誘導体より製造でき、或いは相互に変換することができる。

【０００９】また本発明化合物においてシス－トランス体、光学異性体、配座異性体等の立体異性体が存在する場合、或いは水和物や錯化合物の状態で存在する場合においても、本発明はそのいずれの立体異性体、水和物、錯化合物をも包含する。

【００１０】次に、本発明化合物の製造方法の一例を述べる。R_1－NH_2、R_2－NH_2又はR_3－NH_2で表される化合物（アミン成分：R_1、R_2及びR_3は各々前記と同じ基を表す）を、例えばグルコース、フラクトース、ガラクトース、マンノース、デオキシグルコース等の六炭糖、グルコサミン、ガラクトサミン等のアミノ糖、サッカロース等のオリゴ糖などの糖類と共存させることにより、本発明化合物を得ることができる。又、アミン成分として、蛋白質、ペプチド類などを用いて混合反応させた後、酸加水分解処理を行い本発明化合物を得ることもできる。

【００１１】反応温度、反応時間、ｐＨ等の反応条件に関しては特別な設定条件はなく、適宜設定することができる。操作上簡単なのは室温に放置しておけばよいが、加熱することなどにより反応を促進できる。得られた本発明化合物は、蒸留、クロマトグラフィー、再結晶等の通常の手段により精製することができる。

【００１２】

【実施例】以下に本発明ピロロナフチリジニウム誘導体の実施例を示すが、本発明はこれによって限定されるものではない。

実施例１．グルコース７９．２ｇとγ－アミノ酪酸（ＧＡＢＡ）４５．３ｇを２５０ｍＭリン酸緩衝液（ｐＨ７．３）１１００ｍｌに溶解し、３７℃で４５日間静置した。反応溶液をスルホン酸型陽イオン交換樹脂／DIAION PK-216 （三菱化成）に添加し、水洗後、２Ｎアンモニア水で溶出した溶液を減圧下４０℃水浴中で濃縮乾固した。乾固物を少量のイオン交換水に溶解した後、イオン交換水で平衡化したAMBERLITE XAD-2 カラム（オルガノ社）に添加し、通過画分を集めた。この画分を濃縮後、DEVELOSIL ODS LOP-45S カラム（野村化学）に添加し、メタノール－トリフルオロ酢酸混合溶液で溶出した。さらにこれを逆相高速液体クロマトグラフィー／STR ODS-IIカラム（島津テクノリサーチ）により分離精製し、立体異性体である化合物１（６５ｍｇ）、化合物２（１８２．９ｍｇ）及び化合物３（３５．５ｍｇ）をそれぞれ単離した。

【００１３】実施例２．グルコース２５．２ｇとα－ア

セチルリジン３４ｇを２５０ｍＭリン酸緩衝液７００ｍｌに溶解し、実施例１と同様の操作を行い、立体異性体である化合物４（２ｍｇ）及び化合物５（３ｍｇ）をそれぞれ単離した。

【００１４】得られた本発明化合物の物性値を以下に示す。尚、上記実施例と同様の方法で１位又は全炭素が^{13}Ｃでラベルされたグルコースを用いてラベル化物質を製造し、構造解析に用いた。蛍光スペクトルは 650-40 Fluorescence Spectrophotometer（日立）により、紫外部吸収（ＵＶ）スペクトルはDU-650 (Beckman)により共にメタノール中で測定した。スパッタードイオン質量分析ペクトル（ＳＩＭＳ）は M-80B（日立）によりマトリックスにグリセリンを用いて測定した。核磁気共鳴（ＮＭＲ）スペクトルは重水中、ARX-500 (Bruker)で測定し、プロトンは共鳴周波数５００．１３ＭＨｚを、^{13}Ｃは共鳴周波数１２５．７７ＭＨｚを０．００ｐｐｍとした。^{1}Ｈ－ＮＭＲスペクトル及び^{13}Ｃ－ＮＭＲスペクトルの帰属は ^{1}Ｈ-^{1}Ｈ　ＣＯＳＹ、ＨＭＱＣなどの２次元ＮＭＲにより決定した。

【００１５】・化合物１

８－ヒドロキシ－１，２，６，７，８，８ａ－ヘキサヒドロ－３－（１，２，３－トリヒドロキシプロピル）－１，４，６－トリス（３－カルボキシプロピル）－ピロロ〔２，３，４－ｄｅ〕〔１，７〕ナフチリジニウム

蛍光スペクトル：EX_{max} = 370 nm, EM_{max} = 450 nm

ＵＶスペクトル：λ_{max} = 237, 276, 360 nm

ＳＩＭＳ：m/z 527

^{1}H-NMR(D_2O)－δ ppm: 1.79(2H, m, H-2‴), 2.04(2H, m, H-2′), 2.13(2H, m, H-2″), 2.33(2H, t, J=7Hz, H-3‴), 2.44(4H, t, J=7Hz, H-3′, 3″), 3.35(2H, m, H-1‴), 3.47(1H, m, H-1′), 3.50(1H, dd, J=14, 2Hz, H-7), 3.59(1H, m, H-1′), 3.63-3.69(4H, m, H-7, 10, 11, 11), 4.33(1H, m, H-1″), 4.68(1H, brs, H-8), 4.68(1H, m, H-1″), 4.83(1H, d, J=14Hz, H-2), 4.98(1H, d, J=1Hz, H-8a), 5.20(1H, d, J=9Hz, H-9), 5.36(1H, dd, J=14, 1Hz, H-2), 7.92(1H, s, H-5)

^{13}C-NMR(D_2O) － δ ppm: 22.2(t, C-2′, 2‴), 27.1(t, C-2″), 31.5(t, C-3‴), 32.2(t, C-3′), 33.3(t, C-3″), 49.4(t, C-1‴), 53.5(t, C-7), 54.5(t, C-1′), 58.6(d, C-8), 59.8(t, C-2, 1″), 63.2(t, C-11), 67.3(d, C-8a), 68.6(d, C-9), 74.6(d, C-10), 126.8(d, C-5), 134.6(s, C-2a), 135.3(s, C-8b), 139.7(s, C-3), 140.8(s, C-5a), 178.8(s, C-4‴), 180.2(s, C-4′, 4″)

【００１６】・化合物２

８－ヒドロキシ－１，２，６，７，８，８ａ－ヘキサヒドロ－３－（１，２，３－トリヒドロキシプロピル）－１，４，６－トリス（３－カルボキシプロピル）－ピロロ〔２，３，４－ｄｅ〕〔１，７〕ナフチリジニウム

蛍光スペクトル：EX_{max} = 370 nm, EM_{max} = 450 nm

ＵＶスペクトル：λ_{max} = 240, 277, 360 nm

ＳＩＭＳ：m/z 527

^{1}H-NMR(D_2O)－δ ppm: 1.82(2H, m, H-2‴), 2.06(2H, m, H-2′), 2.12(2H, m, H-2″), 2.35(2H, t, J=7Hz, H-3‴), 2.46(4H, t, J=7Hz, H-3′, 3″), 3.33(1H, ddd, J=14, 7, 7Hz, H-1‴), 3.42(1H, ddd, J=14, 7, 7Hz, H-1‴), 3.48(1H, m, H-1′), 3.49(1H, dd, J=14, 2Hz, H-7), 3.61(1H, m, H-1′), 3.68(1H, dd, J=14, 1Hz, H-7), 3.69(1H, ddd, J=9, 3, 3Hz, H-10), 3.73(1H, dd, J=3, 3Hz, H-11), 3.76(1H, dd, J=3, 3Hz, H-11), 4.39(1H, m, H-1″), 4.68(1H, d, J=2Hz, H-8), 4.79(1H, m, H-1″), 4.89(1H, d, J=14Hz, H-2), 5.01(1H, d, J=2Hz, H-8a), 5.06(1H, d, J=14Hz, H-2), 5.21(1H, d, J=9Hz, H-9), 7.95(1H, s, H-5)

^{13}C-NMR(D_2O) － δ ppm: 21.8(t, C-2‴), 22.2(t, C-2′), 26.8(t, C-2″), 31.5(t, C-3‴), 31.8(t, C-3′), 32.0(t, C-3″), 49.8(t, C-1‴), 53.9(t, C-7), 54.3(t, C-1′), 58.8(t, C-1″), 60.4(d, C-8), 61.1(t, C-2), 63.7(t, C-11), 67.7(d, C-8a), 69.0(d, C-9), 74.8(d, C-10), 127.3(d, C-5), 134.5(s, C-2a), 135.1(s, C-8b), 141.1(s, C-3, 5a), 178.0(s, C-4′, 4‴), 178.8(s, C-4″)

【００１７】・化合物３

８－ヒドロキシ－１，２，６，７，８，８ａ－ヘキサヒドロ－３－（１，２，３－トリヒドロキシプロピル）－１，４，６－トリス（３－カルボキシプロピル）－ピロロ〔２，３，４－ｄｅ〕〔１，７〕ナフチリジニウム

蛍光スペクトル：EX_{max} = 373 nm, EM_{max} = 452 nm

ＵＶスペクトル：λ_{max} = 239, 278, 360 nm

ＳＩＭＳ：m/z 527

^{1}H-NMR(D_2O)－δ ppm: 1.84(2H, m, H-2‴), 2.03(2H, m, H-2′), 2.12(2H, m, H-2″), 2.35(2H, t, J=7Hz, H-3‴), 2.46(4H, m, H-3′, 3″), 3.31(1H, ddd, J=14, 7, 7Hz, H-1‴), 3.39(1H, ddd, J=14, 7, 7Hz, H-1‴), 3.46(1H, dd, J=14, 1Hz, H-7), 3.50(1H, m, H-1′), 3.78(1H, dd, J=14, 3Hz, H-7), 3.70-3.79(4H, m, H-10, 11, 11, 1′), 4.32(2H, m, H-8, 1″), 4.78(1H, m, H-1″), 4.79(1H, d, J=10Hz, H-8a), 4.83(1H, d, J=14Hz, H-2), 5.08(1H, d, J=14Hz, H-2), 5.22(1H, d, J=9Hz, H-9), 7.93(1H, s, H-5)

^{13}C-NMR(D_2O) － δ ppm: 21.8(t, C-2‴), 22.1(t, C-2′), 26.6(t, C-2″), 31.3(t, C-3‴), 31.6(t, C-3′), 31.8(t, C-3″), 49.6(t, C-1‴), 54.0(t, C-7), 55.7(t, C-1′), 60.2(t, C-2), 60.4(t, C-1″), 63.5(t, C-11), 63.9(d, C-8), 69.0(d, C-9), 70.4(d, C-8a), 74.7(d, C-10), 127.7(d, C-5), 134.1(s, C-2a), 135.2(s, C-8b), 141.4(s, C-5a, 3), 177.7(s, C-4‴), 177.7(s, C-4′), 178.8(s, C-4″)

【００１８】・化合物４

８－ヒドロキシ－１，２，６，７，８，８ａ－ヘキサヒドロ－３－（１，２，３－トリヒドロキシプロピル）－１，４，６－トリス〔６－（Ｎ－アセチル－Ｌ－ノルロイシル）〕－ピロロ〔２，３，４－ｄｅ〕〔１，７〕ナフチリジニウム

蛍光スペクトル：EX_{max} = 374 nm, EM_{max} = 452 nm

ＵＶスペクトル：λ_{max} = 237, 277, 360 nm

ＳＩＭＳ：m/z 782

^{1}H-NMR(D_2O)－δ ppm: 1.40(6H, m, H-3', 3", 3"'), 1.68(2H, m, H-2"'), 1.72(4H, m, H-2', 2"), 1.84(6H, m, H-4', 4", 4"'), 1.98(3H, s, AcO"'-Me), 1.99(3H, s, AcO'-Me), 2.00(3H, s, AcO"-Me), 3.41(1H, m, H-1'), 3.53(2H, m, H-1"'), 3.61(1H, dd, J=14, 1Hz, H-7), 3.62(1H, m, H-1'), 3.74(1H, dd, J=14, 1Hz, H-7), 3.79(3H, m, H-10, 11, 11), 4.23(3H, m, H-5', 5", 5"'), 4.42(1H, m, H-1"), 4.70(1H, s, H-8), 4.70(1H, m, H-1"), 4.89(1H, d, J=14Hz, H-2), 5.07(1H, d, J=1Hz, H-8a), 5.22(1H, d, J=9Hz, H-9), 5.41(1H, dd, J=14, 1Hz, H-2), 7.95(1H, s, H-5)

^{13}C-NMR(D_2O)－δ ppm: 22.6(q, AcO'-Me, AcO"-Me, AcO"'-Me), 22.8(t, C-2'), 23.1(t, C-2"', 3', 3"'), 25.4(t, C-3"), 26.0(t, C-2"), 30.8(t, C-4'), 30.9(t, C-4"'), 31.3(t, C-4") 49.9(t, C-1'), 53.4(d, C-5', 5"'), 53.6(d, C-5"), 54.6(t, C-7, 1"'), 58.5(d, C-8), 60.5(t, C-1"), 60.8(t, C-2), 63.1(t, C-11), 67.3(d, C-8a), 68.6(d, C-9), 74.4(d, C-10), 126.6(d, C-5), 134.0(s, C-2a), 134.3(s, C-8b), 140.1(s, C-3), 140.7(s, C-5a), 175.1(s, C-6'), 175.1(s, C-6"'), 175.2(s, C-6"), 176.6(s, AcO'-CO), 176.7(s, AcO"'-CO), 176.8(s, AcO"-CO)

【００１９】・化合物５

８－ヒドロキシー１，２，６，７，８，８ａ－ヘキサヒドロー３－（１，２，３－トリヒドロキシプロピル）－１，４，６－トリス〔６－（Ｎ－アセチル－Ｌ－ノルロイシル）〕－ピロロ〔２，３，４－ｄｅ〕〔１，７〕ナフチリジニウム

蛍光スペクトル：EX_{max} = 376 nm, EM_{max} = 452 nm

ＵＶスペクトル：λ_{max} = 239, 278, 360 nm

ＳＩＭＳ：m/z .782

^{1}H-NMR(D_2O)－δ ppm: 1.39-1.48(6H, m, H-3', 3", 3"'), 1.66(2H, m, H-2"'), 1.73(4H, m, H-2', 2"), 1.89(6H, m, H-4', 4", 4"'), 1.98(3H, s, AcO"'-Me), 1.98(3H, s, AcO'-Me), 2.00(3H, s, AcO"-Me), 3.39(1H, m, H-1"'), 3.44(1H, m, H-1"'), 3.50(1H, m, H-1'), 3.57(1H, dd, J=14, 2Hz, H-7), 3.65(1H, m, H-1'), 3.73(1H, dd, J=14, 1Hz, H-7), 3.81(3H, m, H-10, 11, 11), 4.27-4.35(4H, m, H-1", 5', 5", 5"'), 4.75(1H, brs, H-8), 4.78(1H, m, H-1"), 4.94(1H, d, J=14Hz, H-2), 5.08(1H, brs, H-8a), 5.09(1H, dd, J=14, 1Hz, H-2), 5.20(1H, d, J=9Hz, H-9), 7.95(1H, s, H-5)

【００２０】

【発明の効果】ＡＧＥとしては幾つかの候補物質がこれまでに報告されており現在も研究が進められている。本発明者やその共同研究者らも、特開平６－７３０５７号及び特開平８－４８６８６号で開示されているようなピリジニウム誘導体やナフチリジニウム誘導体を見い出していたが、これらはジアミンの縮合二環系を基本母核としていた。本発明ピロロナフチリジニウム誘導体は従来の化合物とは異なり、トリアミンの縮合三環系を基本母核とするものであり、生体内蛋白質との架橋可能な部位が３ケ所あるというその新規な構造から、全く新しいＡＧＥ候補物質として非常に注目すべきものである。

【００２１】従って、従来報告されてきたＡＧＥ化合物と同様に、本発明化合物を指標として、糖尿病及び糖尿病性腎症、糖尿病性動脈硬化症、糖尿病性神経障害、糖尿病性白内障、糖尿病性網膜症、糖尿病性細小血管障害等の糖尿病性合併症並びに老化やそれに伴う疾患等の診断が可能であり、さらにインビトロ及びインビボ試験系において本発明化合物を指標として薬効評価等を行うことができる。また、本発明化合物をハプテンとして作成された抗体は、前述の診断や薬効評価において免疫化学的且つ免疫組織化学的に利用でき、非常に有用性が高い。上述したように本発明ピロロナフチリジニウム誘導体は既知のＡＧＥとは明らかに異なるトリアミンの縮合三環系骨格である新規物質であり、これまでのＡＧＥ候補物質とは違った生体内での存在や生物活性が示唆され、異なった有用性も期待できる。